REMARKS

Applicant acknowledges receipt of the Office Action mailed July 28, 2004.

As explained below, Applicant submits that the amendment of Claim 105 is sufficient to overcome both of the outstanding prior art rejections.

Written description support for the amendment of Claim 105 can be found in the Specification as originally filed. The Specification describes, beginning on page 14 at line 29 and extending to page 15 at line 4, that pseudo target is preferentially present at a higher copy number relative to the target polynucleotide in amplification reactions. Beginning on page 24 at line 10 and extending to page 25 at line 7, the Specification describes the relationship between the amount of pseudo target included in an amplification reaction and the threshold of detectability for the analyte polynucleotide. Example 1 and Table 1 specifically address the effect of increasing pseudo target levels on analyte amplicon production, and provide a basis for the reduction of analyte amplicon production recited in amended Claim 105. Page 52 at lines 5-10 generally discusses "tuning" amplicon production using pseudo targets.

Claims 105-106, 108-110 and 116 remain pending following entry of this Amendment.

Entry of this Response is respectfully requested.

The Rejection Under § 102(b)

Claims 105-106, 109-110 and 116 have been rejected under 35 U.S.C. § 102(b) as anticipated by the content of a journal article by Rosenstraus et al., ("**Rosenstraus**") which discloses co-amplification and detection of a target polynucleotide and an internal control ("IC") polynucleotide. According to the reference, the two amplicon species are synthesized using a

common primer set, and are detected using different probes. As explained below, the instant claims recite limitations on the amount of pseudo target used in the invented method, and so distinguish over the **Rosenstraus** disclosure.

I. The Principle of Operation Underlying the Rosenstraus Reference Requires the Use of Low Levels of IC Polynucleotide

Rosenstraus teaches the use of low levels of an IC polynucleotide for improving the sensitivity of tests based on nucleic acid amplification. Indeed, **Rosenstraus** describes how an IC polynucleotide can be used to identify inhibitory samples for retesting (first paragraph of Results), and particularly states in the second full paragraph under col. 1 of page 193:

> "The **purpose** of the IC is to maximize test sensitivity by identifying inhibitory (i.e., nonamplifiable) specimens that have the potential to generate false-negative results." [Emphasis added]

Rosenstraus emphasizes the purposeful use of only 20 copies of the IC in amplification reactions (see Abstract; second full sentence under col. 2 on page 191; legend of Fig. 1) to assure amplification sufficient to generate a positive signal from very small quantities of target. **Rosenstraus** specifically warns against using higher levels of IC in amplification reactions under the third paragraph of the Discussion section, where it is stated:

> "The IC is used at a concentration of 20 copies per test sample to monitor amplification **at the limit of test sensitivity**. PCR inhibitors decrease amplification efficiency, thereby reducing the amount of PCR product generated from each target molecule. A high target load can compensate for reduced amplification efficiency, yielding enough product to generate a positive signal. **If used at a higher concentration, the IC might not detect weak inhibition that could cause false-negative results at extremely low target loads.**" [Emphasis added]

Thus, **Rosenstraus** both describes a procedure wherein IC polynucleotides are used in amplification reactions at the limit of assay sensitivity, and counsels against the use of substantially higher levels of IC. There is no guidance to depart from this instruction, and any suggestion to do so would change the principle of operation which underlies the teaching of the reference.

II. The Principle of Operation Underlying the Instant Invention Requires the Use of Pseudo Target in Amounts Exceeding the Threshold of Assay Sensitivity

The instantly claimed invention requires the use of high levels of pseudo target, and so goes opposite the guidance provided by **Rosenstraus**. The Specification on page 24 starting at line 10 discusses how selection of the amount of pseudo target can be influenced by the magnitude of amplification, the starting number of analyte polynucleotides, and the sensitivity of the amplicon detection system. This part of the Specification particularly addresses the relationship between amounts of pseudo targets that can be used in an assay and the threshold of detectability for that assay. Based on this disclosure, the amount of pseudo target used in the invented method is generally greater than the amount of analyte polynucleotide to be detected by a positive result in the assay, or the "pre-determined value" recited in the instant claims.

The experimental procedure described in Example 1, together with the results presented in Table 1 illustrate how varying the amount of pseudo target in an amplification reaction can control analyte amplicon production. The trial conducted using 60 copies of the BH10 analyte polynucleotide and 1.0×10^6 copies of the IAC-Ascr pseudo target reduced analyte amplicon production to a level that was 44% of the level achieved when the same reaction was conducted in the absence of pseudo target (see Table 1). Notably, the amount of pseudo target used in this instance must have exceeded the threshold of assay sensitivity by a minimum of 16,600 fold. Use of IC at this level is unquestionably inconsistent with the teaching of **Rosenstraus** because it would defeat the ability to detect weak inhibition that could cause false-negative results at

extremely low target loads near the threshold of assay sensitivity.

Conclusion

The present invention cannot be anticipated by the disclosure of **Rosenstraus** because instantly amended Claim 105 recites limitations that cannot be derived from the cited reference. More specifically, the reference does not disclose the use of IC polynucleotides in amounts that exceed the threshold of assay sensitivity, and certainly does not disclose the use of IC at levels sufficiently high to reduce analyte amplicon production to less than 44% of the amount that would be produced in a reaction conducted in the absence of pseudo target. Rather than suggesting any benefit could be achieved by employing very high levels of IC, **Rosenstraus** teaches the opposite by requiring low levels of IC in reactions so that amplification of the IC will be sufficient to generate a positive signal from targets present at the limit of test sensitivity. Accordingly, **Rosenstraus** actually teaches away from the instantly claimed invention which is both novel and nonobvious in view of the reference. For these reasons, Applicant requests withdrawal of the rejection under § 102(b).

The Rejection Under § 103

Rosenstraus et al., and Kricka

Claim 108 has been rejected under 35 U.S.C. § 103(a) as *prima facie* obvious over the disclosure of the **Rosenstraus** article in view of an article by Kricka, ("**Kricka**"). The rejection essentially states that, because **Rosenstraus** discloses methods of amplifying an internal control polynucleotide, and because **Kricka** describes sensitive detection systems based on luminometry, it would have been obvious to use the method of **Rosenstraus** in accordance with **Kricka** to result in the invention of Claim 108.

Claim 108 incorporates the nonobvious limitations recited in amended Claim 105, and so also is nonobvious. Amended Claim 105 requires that the pseudo target is employed at very high levels, an aspect of the invention which actually goes opposite guidance appearing in the **Rosenstraus** article, and which is discussed above. **Kricka** says nothing to suggest that it would be a good idea to defy the teaching of the **Rosenstraus** and use IC at high levels that might not detect weak inhibition that could cause false-negative results at extremely low target loads. Absent that teaching, the invention defined by Claim 108 cannot be considered obvious in light of the prior art. Accordingly, withdrawal of the rejection under 35 U.S.C § 103 in light of **Rosenstraus** in view of **Kricka** is respectfully requested.

CONCLUSION

In view of the above, it is submitted that the claims are in condition for allowance. Reconsideration and withdrawal of all outstanding rejections are respectfully requested. Allowance of the claims at an early date is solicited. If any points remain that can be resolved by telephone, the Examiner is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

GEN-PROBE INCORPORATED

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By: _____

Michael J. Gilly
Registration No. 42,579
Agent of Record
Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121
(858) 410-8657